REMARKS

Reconsideration of this application, as amended, is respectfully requested.

The indication of allowable subject mater in claims 21 and 26 is gratefully acknowledged. Claim 19 has been amended to incorporate the subject matter of claim 21, and claim 24 has been amended to incorporate the subject matter of claim 26. It is, therefore, believed that these claims and their dependent claims are allowable.

Claims 30-32 have been canceled in view of the restriction requirement.

It is believed that the amendments to the claims overcome the objections to claims 23, 28 and 29.

Claims 18, 23, 24 and 33 were rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse.

Attached are experimental data for Example 5. The data show that after 14 days implants were isolated and underwent histological analysis. Implants with increasing amounts of MIA protein were bigger in overall size and histological analysis revealed highly stimulated cartilage formation in these specimens. The extent of cartilage formation was directly linked to the concentration of MIA applied to the implants. Given the directives of Example 5 and the subsequent data, it is respectfully submitted that the rejected claims are enabled. A declaration of Dr. Carola Dony will be submitted to verify this data.

Claims 19, 20, 22, 25 and 27-29 were rejected under 35 U.S.C. §112, first paragraph for allegedly containing subject matter that was not described in the specification in such a way to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. Applicants respectfully traverse.

The Examiner objects primarily to the breadth of the term osteoinductive protein. However, as the Examiner notes, Applicants have identified BMPs and hedgehog proteins as such proteins. The Examiner argues that these classes of proteins are not structurally related, but it is not necessary to do so. The proteins are described as functionally related, and a protein may

be tested to see if it is osteoinductive according to known techniques, such as how BMPs were identified as possessing such a quality.

In addition, attached are a list of references citing various osteoinductive or osteogenic compounds, showing that one skilled in the art can readily identify such proteins. Examples are bFGF, dpp and 60A, TGF-beta 1, GDF5. Note that dpp and 60A are Drosophila proteins that work in mammals, and those of skill in the art were still able to determine that they induce endochondral bone formation in mammals. In view of the foregoing, it is clear that one skilled in the relevant art would not have any difficulty identifying osteogenic proteins, and in fact, many have already done so. Withdrawal of this rejection is respectfully requested.

Claims 18 and 23 were rejected as allegedly obvious over Bogdahn in view of Beck. Claims 18 and 23 were also rejected as allegedly obvious over Bogdahn in view of the 1992 BioRad catalogue ("BioRad"). Applicants respectfully traverse.

As the examiner states, the '929 patent suggests matrices of polyanhydrides may be used as a delivery system for antigens to produce antibodies in animals. The mere fact that an antigenic protein can be combined with a three dimensional matrix material such as described in '929 does not lead one to incorporate MIA with such a matrix material simply because MIA antibodies might be prepared in such a manner and could be useful.

The same applies for the combination of the '366 patent with the 1992 BioRad catalogue. Furthermore, it only provides a laundry list of suggested materials to purify proteins. There is certainly no motivation to combine MIA with a matrix to yield a pharmaceutical composition.

At a minimum, the cited references are limited to their specific matrix materials and do not teach or suggest others as noted by the examiner at page 4 of the Office Action. Claim 37 is consistent with the Examiner's position that the Markush group of matrix materials therein are not taught or suggested by the cited references.

In view of the foregoing, withdrawal of all rejections and allowance of this application are respectfully requested.

If any fees are due to enter this response, authorization is given to charge deposit account No. 50-0624.

Respectfully submitted,

FULBRIGHT & JAWORSKI L.L.P.

By _____
James R. Crawford
Reg. No. 39,155

666 Fifth Avenue
New York, NY 10103
(212) 318-3148
Encl.

BMP2-7:
Hotz, G., and Herr, G. (1994). Bone substitute with osteoinductive biomaterials - current and future clinical applications. International Journal of Oral & Maxillofacial Surgery *23*, 413-417.
Wozney, J. M., Rosen, V., Byrne, M., Celeste, A. J., Moutsatsos, I., and Wang, E. A. (1990). Growth factors influencing bone development. Journal of Cell Science - Supplement *13*, 149-156.
Wang, E. A. (1993). Bone morphogenetic proteins (BMPs): therapeutic potential in healing bony defects. Trends In Biotechnology *11*, 379-383.

OIF:
Hetz, G., and Herr, G. (1994). Bone substitute with osteoinductive biomaterials - current and future clinical applications. International Journal of Oral & Maxillofacial Surgery *23*, 413-417.

GDF5:
Hotten, G. C., Matsumoto, T., Kimura, M., Bechthold, R. F., Kron, R., Ohara, T., Tanaka, H., Satoh, Y., Okazaki, M., Shirai, T., *et al.* (1996). Recombinant human growth/differentiation factor 5 stimulates mesenchyme aggregation and chondrogenesis responsible for the skeletal development of limbs. Growth Factors *13*, 65-74.

bFGF:
Wang, J. S. (1996). Basic fibroblast growth factor for stimulation of bone formation in osteoinductive or conductive implants [Review]. Acta Orthopaedica Scandinavica *67*, 1-33.
Wang, J. S., and Aspenberg, P. (1993). Basic fibroblast growth factor and bone induction in rats. Acta Orthopaedica Scandinavica *64*, 557-561.
Wiltfang, J., Merten, H. A., and Wiltfang, J. (1996). Ectopic bone formation with the help of growth factor bFGF. Journal of Cranio Maxillo Facial Surgery *24*, 300-304.

dpp und 60A :
Sampath, T. K., Rashka, K. E., Doctor, J. S., Tucker, R. F., and Hoffmann, F. M. (1993). Drosophila transforming growth factor β superfamily proteins induce endochondral bone formation in mammals. Proc Natl Acad Sci U S A *90*, 6004-6008.

TGF-beta 1:
Ripamonti, U., Duneas, N., Vandenheever, B., Bosch, C., and Crooks, J. (1997). Recombinant transforming growth factor-beta-1 induces endochondral bone in the baboon and synergizes with recombinant osteogenic protein-1 (bone morphogenetic protein-7) to initiate rapid bone formation. Journal of Bone & Mineral Research *12*, 1584-1595.

shh:
Kinto, N., Iwamoto, M., Enomoto-Iwamoto, M., Noji, S., Ohuchi, H., Yoshioka, H., Kataoka, H., Wada, Y., Yuhao, G., Takahashi, H. E., *et al.* (1997). Fibroblasts expressing Sonic hedgehog induce osteoblast differentiation and ectopic bone formation. Febs Letters *404*, 319-323.

2) Osteogene Faktoren:

PDGF-BB, EGF, IGF-I, TGFbeta1-3

Giannobile, W. V. (1996). Periodontal tissue engineering by growth factors. Bone *19*, 37.

PDGF, IGF-I, IGF-II, TGFbetas
Reddi, A. H., and Cunningham, N. S. (1990). Bone induction by osteogenin and bone morphogenetic proteins. Biomaterials *11*, 33-34.

Example 5

Mouse bioassay for cartilage, bone, tendon and ligament induction

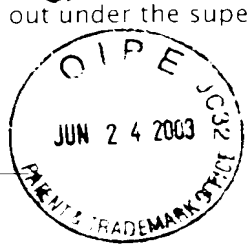
Similar to the Sampath and Reddi rat ectopic implant assay, a mouse ectopic implant assay, using outbred NMRI mice, 4 months old was performed (Sampath and Reddi, Proc. Natl. Acad. Sci. USA 80 (1983) 6591-695: WO 95/16035). (a) MIA alone, (b) BMP-2 alone and (c) combinations of MIA and BMP-2 were applied in the appropriate buffer, 0.1% trifluoroacetic acid for BMP-2 and 100 mM potassium-phosphate, 150 mM NaCl, pH 6.0 for MIA. As carrier were used collagen type I matrix and hyaluronic acid. Any suitable carrier maybe used, e.g. collagen type I matrix, collagen-heparin mixture, gelatine capsules, hyaluronic acid, alginate or other functionally equivalent device, based on biocompatibility, biodegradability, stability and mechanical properties.

The implants were placed intramuscular into the gluteus muscle of the mouse and left for 14 days. After 14 days the mice were sacrificed by cervical dislocation. The implants were isolated and processed using standard histological techniques (see Theory and Practice of Histological Techniques, ed. Bancroft and Stevens, Churchill Livingstone, 1996). Paraffin sections (4-7 µm) were cut and stained with von Kossa/Toluidine blue to visualize and quantitate the amount of cartilage and bone tissue induced in each implant. Positive (e.g. BMP-2) and negative (e.g. mock device) implant control groups were compared to experimental implants.

To assess the quality of cartilage and/or bone induced, gene expression can be studied by RNA in situ hybridization for cartilage and bone markers as described above, using cartilage markers (e.g. collagen II, collagen X) and bone markers (e.g. collagen I, osteocalcin).

After 14 days implants were isolated and underwent histological analysis. Implants containing osteoinductive factor alone were smaller in size and only bone with bone marrow and fibrous tissue could be detected in the histological sections. No cartilage tissue could be detected (fig. 1B). In contrast, implants with increasing amounts of Mia protein were bigger in overall size and histological analysis revealed highly stimulated cartilage formation in these specimens (fig. 1D). The extent of cartilage formation was directly linked to the concentration of Mia applied to the implants (fig. 2). In implants with more than 10 µg Mia (combined to 1 µg of the osteoinductive protein BMP2) very high extent of cartilage tissue was detected, resulting from prolonged cartilage formation rate and inhibition of bone formation. No bone formation was detectable in these implants.

Experiments were carried out under the supervision of:



Dr. Gabriele Protzel

Dr. Carola Dony